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Perceptions of Equipoise, Risk–Benefit Ratios, and "Otherwise Healthy Volunteers" in the Context of Early-Phase HIV Cure Research in the United States: A Qualitative Inquiry

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Abstract

Early-phase HIV cure research is conducted against a background of highly effective antiretroviral therapy, and involves risky interventions in individuals who enjoy an almost normal life expectancy. To explore perceptions of three ethical topics in the context of HIV cure research—(a) equipoise, (b) risk–benefit ratios, and (c) "otherwise healthy volunteers"—we conducted 36 in-depth interviews (IDIs) with three groups of purposively selected key informants: clinician-researchers (n = 11), policy-makers and bioethicists (n = 13), and people living with HIV (PLWHIV; n = 12). Our analysis revealed variability in perceptions of equipoise. Second, most key informants believed there was no clear measure of risk–benefit ratios in HIV cure research, due in part to the complexity of weighing (sometimes unknown) risks to participants and (sometimes speculative) benefits to science and society. Third, most clinician-researchers and policy-makers/bioethicists viewed potential HIV cure study participants as "otherwise healthy volunteers," but this perception was not shared among PLWHIV in our study.

Keywords

equipoise, risk–benefit ratios, "otherwise healthy volunteers," HIV cure research, United States

Introduction

Early-phase HIV cure research is conducted against a background of highly effective antiretroviral therapy and involves risky interventions in individuals who enjoy an almost normal life expectancy (Food and Drug Administration [FDA], 2013; Lo & Grady, 2013). The FDA defines HIV cure research as

> any investigation that evaluates: 1) a therapeutic intervention or approach that controls or eliminates HIV infection to the point that no further medical interventions are needed to maintain health; and 2) preliminary scientific concepts that might ultimately lead to such a therapeutic intervention. (FDA, 2013)

HIV cure research encompasses several modalities, including, but not limited to, cell and gene modification, reactivation of latently infected cells, immune-based therapies, including the use of biomedically engineered antibodies or molecules, early antiretroviral treatment (including pediatric HIV cure research), as well as combinatorial approaches (Deeks et al., 2016). These investigational strategies involve high risks, provide limited clinical benefits for participants, and pose ethical challenges similar to other early-phase

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clinical research (Dresser, 2017; Dubé, Henderson, & Margolis, 2014; Lo & Grady, 2013; Sugarman, 2013; Tucker & Rennie, 2014).

A key condition for moving promising interventions forward rests in the theoretical and empirical grounds for proceeding with clinical research (Dresser, 2017). The term *equipoise* was introduced by philosopher Charles Fried to denote the "controversy within the scientific community about whether the new intervention is better than standard therapy" (Emanuel, Wendler, & Grady, 2013; Kottow, 2009). The fact that most people living with HIV (PLWHIV) are doing well on antiretroviral treatment (Eholié et al., 2016), and have safe and easily administered alternatives to cure research participation (Eyal, 2017a), may raise questions related to equipoise and whether this concept can be used to evaluate early-phase HIV cure research protocols. Any disruption to the standard of care, which at this point means early and lifelong antiretroviral therapy (INSIGHT START Study Group, 2015), or potential risks above standard HIV therapy, generates scientific uncertainty or controversy (Dresser, 2017).

Assessment of risks and benefits are two main hallmarks in any ethical decision to approve clinical research. "Research risks must be minimized and acceptable in relation to the prospective benefits to study participants or of the knowledge to be generated" (Lo & Grady, 2013). Risks are defined in terms of the magnitude and "probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study," while benefits are "valued or desired outcome[s]" (University of California, Irvine, 2017). Early-phase HIV cure experiments typically involve significant risks that must be justified in the context of effective and safe antiretroviral treatment, including the risks of the intervention, the risks of sometimes invasive study procedures, the risks of treatment interruption, if indicated in the protocol, not to mention possible psychological, legal, social, and financial risks (Eyal, 2017a). In addition, because early-phase HIV cure studies usually represent experiments with little to no therapeutic or curative intent (Dubé et al., 2014),[1] risk–benefit ratios might not be favorable for the individual study participants, but might be favorable for the field of HIV cure research as a whole. This is true for all Phase I clinical research.

While risks exceed benefits in early translational HIV cure research, the general FDA policy is to consider most potential HIV cure study volunteers as being "otherwise healthy volunteers." The agency uses the term for the purpose of assessing risks versus benefits in clinical trials (Forum for Collaborative HIV Research, 2014). The term "otherwise healthy volunteers" is used because most HIV cure research participants are well-treated, virally suppressed, relatively immunocompetent and often have undetectable HIV (FDA, 2014). Yet, HIV cure interventions have generally been cancer drugs used in very sick cancer patients—repurposed as HIV latency-reversing agents, for example. The healthiest volunteers may arguably have the most to lose in terms of current and future health, or the least to gain from participating in research with little apparent benefit. The issue of "otherwise healthy volunteers," while also relevant to other human clinical research, such as healthy recipients of organ transplants (Hutchinson & Geissler, 2015), received heightened attention recently in the context of HIV cure research. In 2015, the FDA placed a study on clinical hold after determining that it presented unacceptable safety risks to "otherwise healthy volunteers." The study involved a repurposed anticancer agent, panobinostat, commercially known as Farydak®[2] to be used in combination with alpha-interferon to reactivate the latent HIV reservoir. The use of a dose used in sick cancer patients for "otherwise healthy people" living with HIV posed an unacceptable safety risk.

In this article, we review three ethical topics in HIV cure research, namely (a) equipoise, (b) risk–benefit ratios, and (c) the notion of "otherwise healthy volunteers." We first present stakeholder perspectives on these concepts, followed by a brief ethical analysis and points of consideration for the field.

Method

Participants

We conducted 36 in-depth interviews (IDIs) with three groups of purposively selected key informants: clinician-researchers (n = 11), policy-makers and bioethicists (n = 13), and PLWHIV (n = 12). Clinician-researchers represented eight U.S. academic centers and a variety of HIV cure research modalities. Policy-makers and bioethicists either represented regulatory agencies or institutional review boards (IRBs) involved in HIV cure research. PLWHIV (seven males and five females) were 18 years of age or older and all were taking HIV treatment and virally suppressed at the time of the interview. At least one had previously volunteered in HIV cure research and all had indicated they may be interested in doing so in the future or wanted to learn more about such research. PLWHIV had previously participated in our survey on willingness to participate in HIV cure research in the United States (Dubé, Evans, et al., 2017). Equipoise was not included in the key informant interview guide for PLWHIV as it reflected a technical and specialized concept.

Data Collection

The lead author conducted the IDIs, lasting between 30 and 75 min, via telephone or in person from September 2015 to January 2016. All IDIs were conducted in English and

audio-recorded, except for one participant who declined recording but accepted note-taking. The interview guides included questions regarding perceptions of equipoise, risk–benefit ratios, and the notion of "otherwise healthy volunteers" as they related to HIV cure research. Interviews were conducted until saturation was achieved, while maintaining a balance in the number of key informants across the three categories.

Ethics Statement

The Non-Biomedical Institutional Review Board (IRB) of the University of North Carolina at Chapel Hill approved the study (Study 14-2672). Key informants provided their oral informed consent to participate and were provided with a copy of the IRB-approved informational sheet.

Data Analysis

We transcribed the recorded interviews verbatim. A research assistant reviewed the transcripts for completeness and accuracy by vetting the audio recordings against the typed transcripts. To protect informants' identities, we redacted all personal identifiers from the transcripts. We used an applied thematic approach to analyze the data, applying both a priori and emergent codes to the data using MAXDQA (version 12.1.3, Berlin, Germany). The principal investigator initially coded the data, and a research assistant subsequently examined code applications in all transcripts to determine agreement with them. Coding discrepancies were resolved via discussions. Coding reports were then reviewed and discussed to identify and reach consensus on the interpretation of the different themes and subthemes within the three general thematic concepts (equipoise, risk–benefit ratios, and "otherwise healthy volunteers"). We then summarized key informants' perceptions around these three ethical topics related to HIV cure research.

Results

Our analysis revealed three main findings. First, there was variability in the perceptions of equipoise. The overall perception was that as in other areas of research, equipoise only applied to late-phase trials involving efficacy. Second, most key informants believed there was no clear measure of risk–benefit ratios in HIV cure research, due in part to the complexity of weighing (sometimes unknown) risks to participants and (sometimes speculative) benefits to science and society. Third, most clinician-researchers and policy-makers/bioethicists viewed potential HIV cure study participants as "otherwise healthy volunteers," but this perception was not shared among PLWHIV in our study.

Equipoise and HIV Cure Research

Clinician-researchers and policy-makers/bioethicists varied in their definitions and perceptions on the role of equipoise in HIV cure research. There was an overall perception that equipoise applied to late-phase efficacy trials, as opposed to HIV cure research in the early phase of experimentation.

From the perspective of clinician-researchers, equipoise was defined as "the concept in a trial . . . [where] you are going in without any preconceived notion that the treatment is going to work or not" (clinician-researcher, #206). Clinician-researchers perceived equipoise as a criterion that allows researchers to randomize study participants from an ethical standpoint, and relates to "questions for which we do not have solid answers" (clinician-researcher, #203). Clinician-researchers explained that in the field of HIV cure research, scientists would need to approach the design of a study with a "reasonable assumption . . . about what we currently know and what we don't know about the way the reservoir can be reactivated and the next step which would be to see [viral] clearance" (clinician-researcher, 210).

A different subgroup of clinician-researchers stated that equipoise did not currently apply to HIV cure research because there are no efficacy data for any of the modalities being investigated. They stressed that equipoise can only be applied when the potential efficacy of at least one of two comparison therapies is known. The example of the START trial (INSIGHT START Study Group, 2015) was given to illustrate where equipoise was applicable, because PLWHIV were randomized to early versus late HIV treatment. The START trial was conducted at a time when the outcome of one approach versus the other was not yet fully settled. By contrast, most current HIV cure research studies are often Phase I studies of new approaches, including first-in-humans studies and investigational new drugs (INDs). They are short-term experiments for which there is no expected therapeutic benefit. Clinician-researchers explained that, given that current antiretroviral treatment is well-characterized, the key implementation and ethical question in HIV cure research becomes clearly communicating potential risks to study participants, and attemping to minimize those risks. Similarly, another clinician-researcher described this thought process in determining the best use of equipoise:

> I use the term a lot in randomized clinical trials to make sure that I feel in my heart and in my head that I could recommend either course of treatment to somebody that I really care for, like a close relative. If I can't do that, if I feel like I should have one treatment versus the other, or that I would want my brother to be treated with one versus the other, then I do not have equipoise. So to me, that is a very important question in a randomized clinical trial. . . . We know the state of current treatment. With investigational treatment, like what are talking about here, there is risk. I would say . . . I would not try to say

> that I have equipoise. . . . The question becomes, given societal needs or potential benefits of finding a cure, with informed consent, would it be ethical for a person to participate in research where the intervention would not be better than the treatment itself. And, you know, people are willing to do different things. . . . They are willing to, for the benefit of society, take a personal risk. And it's our responsibility as investigators to make sure that we are designing trials that limit the risks as much as possible and that are communicating all we can to the participants. (Clinician-Researcher, #211)

Correspondingly, some of the clinician-researchers reported that HIV cure studies up to this point have not used double-blind, placebo-controlled designs, so equipoise has not been a practical concept in early-phase HIV cure research, especially for gene modification studies that do not have control arms. Unless an investigator is trying to prove noninferiority, for example, Highly Active Antiretroviral Therapy (HAART) versus megaHAART as in some early antiretroviral treatment trials, these clinician-researchers reported that equipoise does not apply.

Like clinician-researchers, policy-makers/bioethicists were split as to the applicability of equipoise in HIV cure research. A number of policy-makers/bioethicists stated that equipoise was somewhat relevant to the HIV cure research field because, it is "an element that we always consider in any research submitted for review by the FDA. There has to be some level of equipoise [and we] cannot quantify that" (policy-maker/bioethicist, #307). Equipoise was perceived by some policy-makers/bioethicists to ensure that studies remain unbiased because scientific questions at hand have not yet been answered. As a result, it promotes a healthy sense of skepticism as to whether the proposed intervention may or may not work. Equipoise was viewed by some policy-makers/bioethicists as being imperative to justify moving a study forward. A policy-maker/bioethicist said that equipoise is "probably the trickiest ethical issue in [his or her] mind, especially [for] someone who is tolerating ART quite well and [has] the infection (. . .) under control" (policy-maker/bioethicist, #310). She or he referred to the infectious disease doctors who may not agree with their patients joining HIV cure studies if their clinical management is under control: "Why take and why forego proven treatments that are well tolerated for the chance that something may be better?" (policy-maker/bioethicist, #310)? She or he forewarned that HIV cure research must be informed with the absolute best available evidence at any given time. Another policy-maker believed equipoise was a useful concept related to the standard of care discussion. For HIV, there is a standard of care for treatment and clinical management of the disease, but no HIV cure standard of care. This key informant asked whether it made sense to allow experimental studies that disrupted standard HIV treatment, and said that equipoise may become more useful when HIV cure interventions start showing signals of efficacy.

In sharp contrast, one policy-maker/bioethicist was adamant that equipoise did not apply to HIV cure or remission research in general. He believed that equipoise was a fallacy that did not necessarily lead to ethical studies:

> I do not believe in the need for equipoise in clinical trials in general. I think it's a mistake of my fellow bioethicists. . . . Equipoise is the concept that before the trial begins the different arms of the trial will not be expected . . . there won't be a difference in the prospects given our partial information about the effectiveness of the interventions . . . and the risks of the intervention. . . . There are trials that would not be ethical even with equipoise. (Policy-Maker/Bioethicist, #312)

In turn, most of the arguments given by policy-makers/bioethicists against the use of equipoise in HIV cure research pertained to the lack of a comparator for an effective cure in the HIV cure research field, a key requirement for equipoise to be applicable. They explained that the field of HIV cure research remains in the early phase of experimentation, and that equipoise is more useful for late-phase randomized controlled trials. The current comparison in HIV cure research is between highly effective HIV treatment (e.g., one pill per day) with an HIV cure research modality of unknown safety and efficacy. A policy-maker/bioethicist pointed out that this is not an "apples to apples comparison" (policy-maker/bioethicist, #305) and cautioned that it is "not fair to ask" (policy-maker/bioethicist, #305) the equipoise question at this time in HIV cure research because we cannot compare an early-phase HIV cure research strategy with a therapy that keeps the study participants virally suppressed and immunologically stable. Compared with HIV prevention research such as HIV vaccine trials, she or he described, these can be justified ethically using equipoise because there are effective prevention methods, such as condoms or preexposure prophylaxis, that can serve as comparators for equipoise. On the HIV cure side, there is no robust comparator. HIV treatment will not cure anyone. As a result, per this policy-maker/bioethicist, any attempt at making a comparison becomes misguided. In HIV cure research, she or he explained, the key question is not so much one of equipoise, but of getting an accurate representation of the risks that people are being asked to incur and how these can be justified vis-à-vis the potential scientific benefits to be gained.

Finally, some of the policy-makers/bioethicists fell somewhere in the middle of the spectrum, saying that whether equipoise applied depended on the study, the intervention, and the population. A policy-maker/bioethicist (#306) explained that equipoise is relevant for some studies but not others, and this is contingent upon the particular protocol. Instead of equipoise, she or he proposed implementing futility rules and safety endpoints that can minimize risks to study participants. For example, she or he

perceived that requiring the intervention to be initially tested in only five participants, and having the first five participants on a treatment interruption study experience a viral rebound within 3 to 4 weeks, would provide a clear futility or safety signal of a cure strategy, adding objectivity and rigor to a study as well as placing as few partipants at risk as possible.

Where there seemed to be convergence between clinician-researchers and policy-makers/bioethicists was that equipoise may not apply to early-phase HIV cure studies (or any other early-phase research trials), as we lack a firm comparator for an effective HIV cure. Equipoise may be more relevant to late-phase randomized clinical trials that test products with potential efficacy and require randomization (or research arms).

Risk–Benefit Ratios and HIV Cure Research

Descriptions varied from the three groups of key informants on what favorable risk–benefit ratios in HIV cure research meant to them. The overarching theme was that risk-benefit assessments are evolving in HIV cure research and must be done on a case-by-case or ongoing basis. Given the complex nature of HIV cure research, informants expressed that it was difficult to derive calculations of risks versus benefits. Despite variability in responses, the balance was tilted toward the perception that HIV cure studies carried greater risks than benefits for the majority of respondents. PLWHIV described risk and benefit assessments to be personal and specific to each individual person and recognized the altruistic and societal benefits of joining HIV cure studies.

Most clinician-researchers stressed the possibility of high risk and corresponding lack of direct clinical benefits in HIV cure research. One said that "the benefits are usually zero [and] it's usually just about the risks" (clinician-researcher, #204). Most clinician-researchers reported that benefits accrue to science and society instead of the individual participants. Therefore, the risk–benefit calculus entails looking at the risks for these unique participants, compared with the benefits in terms of knowledge for society. In the absence of potential known clinical benefits, it was explained that the thresholds of safety and efficacy remain high for allowing an HIV cure research intervention to move forward. For the most part, clinician-researchers agreed that it was premature to try to create anything resembling a clear risk–benefit ratio in HIV cure research. A clinician-researcher explained the complexity of making risk–benefit assessments in HIV cure studies given the incremental nature of the research:

> I hope nobody has a real answer to that. I don't think it's easy to imagine having a simple equation that can take you there. . . . [We] know the risks and benefits of conventional treatment. We don't really know all of them yet, obviously, but to me, one of the issues here is that . . . it's unlikely that many investigators with some of the trials that are going on now would expect those trials to right there find a cure. . . . Most of us expect that . . . the trials that we do in this part of the epidemic will give us incremental information. . . . But, if they are well designed, and well conducted and well analyzed, they will move us along to making progress. So the risks and benefits to the participant in that setting is that I am willing to ask somebody to take a risk . . . that this will ultimately move us to the point where we do have a cure. The benefits are more ultimate and societal than they are individual and immediate. But how do you really put a number on that, that's really hard. (Clinician-Researcher, #211)

This quote demonstrates that evaluating risks and benefits in HIV cure research is difficult, given the experimental incrementalism involved. The viewpoint was emblematic of the perceptions of other clinician-researchers, who believed that HIV cure experiments were scaffolds to inform subsequent sets of experiments. Furthermore, while the risks of HIV cure research accrue to the individual research participants, the potential benefits are societal. The majority of clinician-researchers referred to the importance of the informed consent process in conveying the lack of direct clinical benefits to potential study volunteers. A clinician-researcher stated that "when investigators write informed consent forms, they should state bluntly that there are no expectations of benefits or cure to the individual participants for the foreseeable future" (clinician-researcher, #206).

Similarly, policy-makers/bioethicists explained that HIV cure research strategies have a risk–benefit profile contingent upon the characteristics of the investigational product/intervention, the type of study participants enrolled, their stage of disease, and the standard of care available. Policy-makers/bioethicists shared similar views as clinician-researchers in that it is difficult to obtain risk–benefit measures for HIV cure studies given the diversity of the approaches and the early phase of the experiments. A number of policy-makers/bioethicists were adamant that HIV cure clinician-researchers must ensure that risks are justified and work toward minimizing those risks. A policy-maker/bioethicist explained the difficulty of performing risk–benefit calculi. She or he said that juxtaposing personal risks with personal psychological benefits would be like comparing apples to oranges:

> Do you mean a number . . . or a concept? . . . I don't think that you would derive a number that would be rationally justified, that we derived in some way by principles of ethics. . . . There are several reasons why we are not there. One is [that we are] comparing apples and oranges. How do you weigh against each other medical harms on one hand and psychosocial benefits on the other? We just in general do not have very good tools for assessing those things. That's one thing. The other thing is that we lack factual information. We do not know the likely impact

> on the psychosocial [dimension] of the person and it is going to be very hard to come up with reliable numbers on this. (Policy-Maker/Bioethicist, #312)

The above narrative is demonstrative of conversations with policy-makers/bioethicists, who explained that risk and benefit assessments in HIV cure research remained difficult to make given that we are dealing with many hypothetical, theoretical, and unknown risks. Furthermore, policy-makers/bioethicists described that the impractical quantitation of various types of risks and benefits, such as psychological risks–benefits, make the calculus even more arduous. A policy-maker/bioethicist rejected the concept of risk–benefit entirely and uniquely preferred to speak in terms of "investments" (policy-maker/bioethicist, #303) toward an HIV cure. She or he asked to move beyond what she or he called the "risk–benefit ratio fallacy" (policy-maker/bioethicist, #303) and referred to case-by-case analyses performed by the FDA to evaluate protocols. Overall, there was consistency across narratives that the field of HIV cure research is rapidly evolving and risks and benefits remain in flux, yet another reason why assessing risk–benefit ratios can be challenging. A policy-maker/bioethicist explained that it is almost impossible to apply a consistent algorithmic approach: "At the end of the day, you have to satisfy yourself that the potential risks outweigh the benefits" (policy-maker/bioethicist, #310).

In general, PLWHIV described risk and benefit assessments as personal and specific to individual study participants. PLWHIV explained that each person has a different risk threshold, and this is compounded with the fact that each HIV cure investigational protocol is unique. Two PLWHIV described their thought processes for how they make risk and benefit evaluations:

> If the research could really make a change as far as the disease is concerned—but maybe it could hurt me, but ultimately there is a 1 in 5 chance, but I happened to be that 1, and if what you could learn from me would totally change the world . . . It's an opportunity to help a situation. (Patient-Participant, #103)

> That's kind of tough for me to answer. They all have some risk, but like everything, it's a calculated risk. The stem cell transplant for me is a bit too risky personally, but the monoclonal antibody would be okay. With the kick and kill strategy, I could afford to take a hit with my virus so I would be willing to have some health repercussions from something like that. So I think that everything has risks, but the most extreme and radical things are what tend to unnerve me. The stem cell transplant for me is extremely radical and I would only undertake it if my life were at serious risk. (Patient-Participant, #111)

Overall, PLWHIV recognized that personal judgments may come into play when making decisions about whether to join HIV cure clinical studies and desired to take calculated risks. PLWHIV also recognized the existence of altruistic and societal benefits of HIV cure research participation. There was variability in the participants' thought process for making risks to benefits calculations in HIV cure research.

"Otherwise Healthy Volunteers" in HIV Cure Research

Clinician-researchers and policy-makers/bioethicists recognized that the advent of highly effacious antiretroviral treatment raised the threshold of safety and efficacy for "otherwise healthy volunteers" who are virally suppressed with well tolerated, easily administered drug regimens and relatively immunocompetent with often undetectable HIV enrolling in HIV cure studies. At odds with the general FDA policy, the majority of PLWHIV interviewed did not consider themselves "otherwise healthy" despite being virally suppressed, and pointed to various medical and life vulnerabilities.

Clinician-researchers recognized that HIV research has made tremendous progress in the past 30 years, allowing PLWHIV to remain relatively healthy. Most described how potent antiretroviral drugs raise the threshold of safety and efficacy for the field of HIV cure research. Two clinician-researchers described that when implementing protocols involving latency-reversing agents, they enrolled healthy participants with high CD4+ counts. Some clinician-researchers provided the nuance that some HIV cure protocols, such as gene modification or stem cell transplants, include individuals experiencing treatment failure or with concurrent lymphomas or cancers that would require a transplant.

A clinician-researcher described "otherwise healthy volunteers" as follows:

> Where we hit some issues today is that patients living with HIV are doing tremendously well. They are living . . . you know . . . a normal life span . . . So the question is how do you think adding on these additional very toxic agents to try to test the concepts of HIV cure, whether it is a latency-reversing agent, a checkpoint inhibitor or a stem cell therapy. How do you go forward in somebody who is doing well clinically and then ask them to take this? . . . So even if you are just going to test a concept you know you want to make sure it is safe and can be given to the patients safely in terms of the fact that these people are doing well and no longer . . . they are no longer going to die in a month or two. They are going to live a healthy life. If they are infected today, they can live up to their 70s. (Clinician-Researcher, #210)

Furthermore, there was a reluctance among policy-makers/bioethicists to expose PLWHIV to risk, because participants have much to lose, including having their health deteriorated as a result of study participation. A policy-maker/bioethicist stated,

> HIV-infected patients who are otherwise healthy and on fully suppressive ART have an anticipated life-span approaching that of HIV-uninfected patients. From the standpoint of assessing risk–benefit, the FDA has consistently stated that it views HIV reservoir research in this otherwise healthy population to be similar to drug research in healthy volunteers. (Policy-Maker/Bioethicist, #311)

A policy-maker/bioethicist explained that the difference between "otherwise healthy volunters" and "unhealthy individuals" goes back to the early days of HIV when no treatment was available. Most PLWHIV, she or he explained, nowadays have access to potent HIV treatment options that allow them to be virally suppressed and lead healthy lives. She or he explained that this also relates to HIV cure studies having no prospect of direct clinical benefits, and this is the reason regulatory bodies remain cautious and risk averse. In turn, most policy-makers/bioethicists recognized that clinician-researchers must walk a delicate balance between the safety of the experimental agents and the efficacy they are hoping for in HIV cure research. For example, "They should not give one dose more or a longer duration of a dose than is necessary to study a proof-of-concept" (policy-maker/bioethicist, #311). In the 2015 panobinostat clinical hold scenario, the dose of the drug was arbitrary. The FDA viewed this as a perfect storm of clinical research problems involving "the combination of a highly toxic drug with potentially life-threatening risks, no anticipated benefit, and insufficient data to know if modifications of trial design, such as lowering dose or total drug exposure, would substantially lower participants' risks" (policy-maker/bioethicist, #311). The barriers of moving HIV cure interventions into humans augment substantially if the participant population is perceived to be "otherwise healthy."

Interestingly, the majority of PLWHIV did not consider themselves "otherwise healthy." They felt that HIV viral suppression or undetectable status was different than being healthy, and perceived themselves as fragile individuals who often still experience great health risks, life challenges, or vulnerabilities. A PLWHIV described health as an illusion for PLWHIV. A few of the PLWHIV referred to comorbidities that are often associated with being HIV-positive that exclude them from HIV clinical studies, for example, hepatitis B and C, mental and psychological issues or complications related to aging, or societal consequences of living with HIV that might affect their health, such as stigma and discrimination. For example, a PLWHIV said, "I keep coming back to the issue of stigma. . . . I feel very vulnerable when it comes to this issue" (patient-participant, #109). Another PLWHIV summarized the challenges associated with conducting risky HIV cure research with "otherwise healthy volunteers" as follows:

> For the younger, healthier ones . . . I don't know. We are going to expose people to modulators, to drugs that are approved for cancer or chemo . . . I know that those doses are a lot lower but there are fears of immune reactivation, lymphoma, cancers, inflammatory issues, auto-immune diseases . . . We don't know. But obviously if we knew, we would not be doing the studies. (Patient-Participant, #102)

Table 1 summarizes the main qualitative findings related to perceptions of equipoise, risk–benefit ratios, and "otherwise healthy volunteers" in early-phase HIV cure research.

Discussion

Our findings provide unique insight into the perspectives of various informants regarding how three ethical concepts relate to early-phase HIV cure research. Narratives revealed possible similarities and differences around these concepts within and between informant types. Perceptions of ethics can play a major role in HIV cure studies, including regulatory and institutional approvals, inclusion and exclusion criteria, design and safety considerations, informed consent, and decisions made by PLWHIV on whether or not to risk their health in the name of research. This article extends the literature in that it provides a preliminary empirical examination of the extent to which traditional ethical domains can be directly applied to early-phase HIV cure research, and the extent to which unique considerations are warranted.

Equipoise and HIV Cure Research

We found that clinician-researchers and policy-makers/bioethicists' perceptions of equipoise in HIV cure research were heterogeneous and reflected variability in understanding of equipoise, as well as disagreements in the research ethics literature. As in other areas of clinical research, the term "equipoise" is usually ascribed to later stage randomized clinical trials involving efficacy (Weijer, 1999) and may not be the appropriate framework for reviewing risks of early-phase research, particularly when "otherwise healthy volunteers" will not clinically benefit. Instead of equipoise, some informants preferred to focus on mitigating HIV cure research risks by having clear futility signals and robust safety rules. The issues of clearly communicating potential risks to study participants and minimizing risks are heightened in HIV cure research, given that most participants are doing well on HIV treatment. HIV cure studies are clearly not disease efficacy trials, but scaffolds to inform subsequent sets of experiments (Dubé et al., 2014).

Nevertheless, some broad advantages of equipoise must be acknowledged. Equipoise may promote a healthy sense of skepticism, prevent redundant research, and define some of the prerequisites for conducting clinical research (Kottow, 2009; Miller & Brody, 2015). Critiques of clinical equipoise have argued that the concept is unnecessary to

Table 1. Summary of Qualitative Findings Related to Perceptions of Equipoise, Risk–Benefit Ratios, and "Otherwise Healthy Volunteers" in Early-Phase HIV Cure Research (United States, 2015-2016).

Perceptions of equipoise in HIV cure research:

- Perceptions of equipoise to assess ethical permissibility of early-phase HIV cure experiments varied among key stakeholders. The overall perception was that equipoise applied to late-phase clinical trials involving efficacy.
- Some clinician-researchers perceived equipoise as a criterion that allows researchers to randomize study participants (most HIV cure-related research experiments do not warrant randomization at this time). Other clinician-researchers, however, perceived that a key implementation and ethical question is the clear communication of potential risks to study participants, and minimization of those risks.
- Policy-makers/bioethicists were split as to the applicability of equipoise in HIV cure-related research. Equipoise was perceived to promote a healthy sense of skepticism and to be a useful concept related to standard of care. Arguments given by policy-makers/bioethicists against the use of equipoise related to the lack of a robust comparator in the HIV cure research field and the inability to compare safe, effective HIV treatment with ineffective investigational curative interventions. A policy-maker/bioethicist was adamantly opposed to the equipoise as an ethical requirement in any clinical research.
- We did not assess perceptions of equipoise among PLWHIV.

Perceptions of risk–benefit ratios in HIV cure research:

- Descriptions varied from the three groups of key informants on what favorable risk–benefit ratios meant.
- Clinician-researchers believed that HIV cure-related research carried greater clinical risks than benefits given the incremental nature of HIV cure research and perceived high thresholds of safety and efficacy in moving HIV cure clinical research forward.
- Policy-makers/bioethicists recognized factors that influenced risks and benefits, including the characteristics of the investigational project/intervention, type of study participants enrolled, stage of disease, standard of care available and potential psychological and emotional benefits of HIV cure research participation.
- Most PLWHIV described risk and benefit assessments as personal and specific to individual study participants and expressed the desire to take calculated risks.

Perceptions of "otherwise healthy volunteers" in HIV cure research:

- Most clinician-researchers and policy-makers/bioethicists viewed potential HIV cure study participants as "otherwise healthy volunteers" given advances in HIV therapy. They recognized that the challenges of moving HIV cure interventions forward augment if participants are virally suppressed and undetectable.
- The perception of being "otherwise healthy" was not shared among PLWHIV due to other medical and life vulnerabilities.

Note. PLWHIV = people living with HIV.

ethically justify clinical trials (Miller & Brody, 2015). In a sense, the concept of equipoise is conflicted because it

> attempts to have it both ways: to view the clinical trial as a scientific experiment, aimed at producing knowledge that can help improve the care of future patients, and as treatment conducted by physicians who retain fidelity to the principles of therapeutic beneficence. (Miller & Brody, 2003, p. 156)

Equipoise would be more applicable to HIV cure research if investigational interventions were more efficacious at depleting the size of the replication-competent HIV reservoir, at preventing viral rebound while off suppressive HIV therapy, or conferring direct clinical benefits.

In the clinical research literature, equipoise has been described as a notion that is biased on the optimism surrounding an intervention (Veatch, 2015). Some scholars would object to asking questions about equipoise altogether, let alone first-in-human or early-phase experiments (Miller & Brody, 2003; Veatch, 2015). While it is beyond the scope of this article to resolve the broader controversy about equipoise in clinical research, most informants in our study found equipoise as not directly applicable to early-phase HIV cure research. In this light, it may be worth exploring alternatives to equipoise, more aligned with early-phase and translational HIV cure research. For example, Miller and Brody proposed that we should carefully investigate all aspects of the design of a clinical study, along with the social and cultural contexts and the motivations of study participants for joining research (Miller & Brody, 2015). Miller and Brody adopted nonexploitation as central to clinical research ethics (Miller & Brody, 2015). Chiong, on the contrary, contended that we should move away from equipoise stating,

> The pertinent question is not whether the two treatments are in equipoise, but instead whether the potential benefits to third parties are sufficient in this case to justify the less-than-optimal care given to some of the patients in the study. (Chiong, 2015, p. 38)

Similar to the general FDA policy of reviewing HIV cure protocols on a case-by-case basis, Kimmelman (2007) proposed using a "modest translational distance criterion" and suggested incorporating an expert study-by-study evaluation. Finally, Joffe and Miller (2008) argued for a close examination of the entire structure of experiments across the translational continuum of biomedical research. There are other normative obligations besides equipoise that govern the work of researchers in the laboratory, at the bench, with animal models and human volunteers—healthy or sick (Joffe & Miller, 2008). This approach may be more suitable

to evaluating early-phase HIV cure research protocols because of its scientific orientation and requirement of methodological rigor. The scientific framework further clarifies the acceptability of invasive research procedures, such as biopsies, that are important to answering scientific questions that may not provide direct benefits to study participants. The entire emphasis remains on professional integrity and scientific value and validity (Joffe & Miller, 2008). Nevertheless, the above concepts reflect the understanding of clinician-researchers and policy-makers/bioethicists toward research. Perspectives of PLWHIV on what should reasonably move forward may differ, particularly as potential study volunteers may be willing to accept greater risks than what biomedical researchers and regulatory authorities would allow to advance scientific knowledge (Dubé, Taylor, et al., 2017; Różyńska, 2015)

Risk–Benefit Ratios and HIV Cure Research

Key informants provided perceptions of risk–benefit ratios in early-phase HIV cure research and expressed there was no perceived quantifiable measure of risks to benefits, especially because risk and benefit assessments remain fluid, contextual, evolving, with no set formula, and performed on a case-by-case basis. Explanations given for the difficulty of evaluating risks and benefits included, among other things, the complexity and incremental nature of HIV cure research, and having to compare asymmetric individual risks with societal benefits.

Risk–benefit ratios require scientific, moral, and personal judgments, as described in the broader ethics literature (Deakin, Alexander, Hooker, & Kerridge, 2013; Emanuel et al., 2013). Our study revealed that, in the context of early-phase HIV cure research, as with other types of research, several factors must enter into the equation, such as the investigational product or intervention, the types of study participants, the stage of disease, and the standard of care available (in this case, potent antiretroviral treatment). Researchers have the responsibility to report potential risks and uncertainties, as well as the inherent lack of direct clinical benefits to participants in early HIV cure experiments, and to ensure that due diligence be undertaken with respect to the informed consent process throughout the course of a study (Henderson, 2015; Lo & Grady, 2013). Furthermore, risks of such early-phase experiments cannot be justified on therapeutic grounds, but by appeal to the scientific value of the research (Anderson & Kimmelman, 2010). Study participants must understand that their participation in HIV cure research rests fundamentally on altruism (Dresser, 2017).

It is apparent from the accounts of PLWHIV we interviewed that personal assessments of risks versus benefits come into play when making decisions about whether to join clinical HIV cure studies. PLWHIV in our study were interested in taking calculated risks, and similar assessments were discussed elsewhere (Dubé, Taylor, et al., 2017; Evans, 2017). Verheggen, Nieman, and Jonkers (1998) have referred to these as "personal balance accounts." Given that potential volunteers weigh expected risks against benefits, HIV cure scientists should have nuanced discussions with potential study volunteers about the possible known and unknown risks of HIV cure research strategies. An open question in early-phase HIV cure research is the extent to which variable perspectives and differing levels of scientific sophistication or degrees of desperation of potential study participants are central to risk and benefit assessments and decisions to move research forward. As discussed elsewhere (Dubé, Taylor, et al., 2017; Gilbertson, 2016), while most informants may start with the assumption that any individual benefit must be clinical in nature, it is possible that study participants value the psychological and emotional benefits of HIV cure research participation. These types of benefits should not be underestimated in early-phase HIV cure research. Activist David Evans (2017) argued that participant values should help guide risk and benefit ratio calculations in HIV cure research. In concordance with the autonomy principle in ethics, Evans insisted that scientists and bioethicists must respect the self-agency of PLWHIV and their capacity to judge risks and benefits based on their own values.

In the broader research ethics literature, Wikler (2017) argued that a favorable risk–benefit assessment can be justifiably based on the comparison between individual risks and social benefits, even if there are no benefits to individual research participants, as long as consent is adequate and there are appropriate safeguards to minimize risks. Instead of the risk–benefit ratio, Weijer called for a "risk-knowledge calculus" to determine whether risks of research can be justified against societal benefits that can be gained from experimentation (Emanuel et al., 2013; Weijer & Miller, 2004). This approach emphasizes the ethical importance of scientific validity and the potential social value of research (Emanuel et al., 2013; Lo & Grady, 2013). Early-phase HIV cure experiments should be designed to answer important specific scientific questions (Lo & Grady, 2013). While the likelihood that there will be any participant benefit is small, there should be a high likelihood that there will be scientific progress that will move the field forward. Finally, Eyal offered a number of approaches to overcome the risk–benefit ratio challenge in HIV cure research, namely (a) reducing risks, (b) enhancing benefits for participants, (c) focusing on free and informed consent, and (d) emphasizing benefits to nonparticipants (Eyal, 2017b). Reasonable ways to address the risk–benefit ratio conundrum are needed in the face of scientific uncertainty in and novelty of HIV cure research, as well as clear criteria for evaluating early-phase HIV cure research protocols fairly. As the number of HIV cure clinical studies is quickly increasing (Treatment Action Group, 2017), more precise information about potential risks is needed. Furthermore,

as the field increasingly embraces a public health and epidemiological approach to HIV cure research, we need to account for individual variations and unpredictability of risks in various participant populations and contexts (Rossouw, Tucker, van Zyl, Sikwesi, & Godfrey, 2017; Smith, Street, Volk, & Fordis, 2013).

"Otherwise Healthy Volunteers" in HIV Cure Research

Like the general FDA policy, most clinician-researchers and policy-makers/bioethicists viewed potential HIV cure study participants as "otherwise healthy volunteers." This perception, however, was not shared among all PLWHIV. How the health status of PLWHIV is described matters. Although they are the best suited to the current first-in-human HIV cure studies, if they are considered "otherwise healthy individuals," exposing them to significantly risky research interventions is controversial from a regulatory and ethical point of view. If they are considered unhealthy individuals, they may be thought to have less to lose from a health standpoint, but may not be best suited to advancing scientific progress in many current HIV cure clinical studies. Less healthy volunteers may also have greater risk for toxicity and serious adverse events and may not respond well to experimental agents (Kuritzkes, 2016), yet they may be the ones who need a cure the most. The choice between "stable" participants and unhealthy participants, as Dresser states, is a fundamental paradox in many early-phase studies, including HIV cure research (Dresser, 2017). In these instances, the ethical principles of risk minimization or nonmaleficence may conflict with the principles of scientific validity and social value. The group of potential volunteers described as "otherwise healthy" is also the group that may arguably have the most to lose in terms of health.

Participant selection for first-in-human HIV cure studies remains a "deep ethical question" (Dresser, 2017). The conundrum "is about selecting for trial participation the least vulnerable population that can usefully answer the research question" (Bretzner, Gilbert, Baylis, & Brownstone, 2011, p. 471). The notion of "otherwise healthy volunteers" may reflect the relative caution regulatory agencies use in approaching studies presenting greater clinical risks in patients who are diseased, yet successfully treated and relatively immunocompetent. The calculus of what is tolerable is obviously different between sick cancer patients than virally suppressed PLWHIV. Nevertheless, as illustrated by responses from PLWHIV in our study, long-term treated HIV disease and undetectable virus by no means represent a perfectly healthy state. Importantly, HIV cure research implementers should also be careful not to produce new vulnerabilities for PLWHIV, especially because HIV cure research requires added burdens, such as frequent study visits and viral load monitoring (Lo & Grady, 2013). There is still a need to evaluate research protocols on a case-by-case and ongoing basis, contingent upon the intervention and the study population, despite a general FDA policy to consider most potential HIV cure research volunteers in the United States as "otherwise healthy" for the purpose of assessing risks and benefits. How study participants are defined also brings about questions of distributive and representational justice in HIV cure-related research. Ensuring that risks and benefits of research are equitably distributed among different populations of PLWHIV pose a great ethical challenge. Those who may need a cure the most may be the least able to contribute to advancing the science, and may be excluded from HIV cure research in greater numbers (Curno et al., 2016).

HIV research has undoubtedly evolved, from the early 1980s when no HIV treatment option was available to today's aspiration of finding interventions that could lead to long-term viral suppression without treatment. Most PLWHIV in the United States are no longer desperately enrolling in clinical studies to gain access to care or latest life-saving drugs (Delaney, 1989; Kuritzkes, 2016). The heterogeneity of HIV cure clinical study designs and interventions and the uncertainty of interventions calls for prudence in exposing "otherwise healthy volunteers" to substantial likelihood of serious risks (Różyńska, 2015).

Table 2 summarizes considerations related to equipoise, risk–benefit ratios, and "otherwise healthy volunteers" in early-phase HIV cure research.

Limitations

This study examined perceptions of ethics concepts related to early-phase HIV cure research among informants in the United States, using qualitative inquiry. The qualitative methodology yielded a rich understanding anchored in the participants' own categories of meaning. We must acknowledge a number of limitations, however. We did not ask about perceptions of equipoise in our sample of PLWHIV. In retrospect, we should have provided a basic definition of "equipoise" and explored general perceptions of the concept among PLWHIV. This would have made our dataset more complete. We only interviewed three types of informants. We did not collect data related to years of experience in HIV cure research from clinician-researchers and policymakers/bioethicists. Few PLWHIV had direct experience participating in HIV cure research. Other significant groups were excluded, such as HIV care providers, pharmaceutical company representatives, or funders. Key informants may not be representative of all those involved in HIV cure research in the United States. It is difficult to ascertain bias in our sample and self-selection may have affected the responses.

Moreover, it is possible that informants' viewpoints were influenced by their sense of responsibility with answering

Table 2. Ethical Considerations Related to Equipoise, Risk–Benefit Ratios, and "Otherwise Healthy Volunteers" in Early-Phase HIV Cure Research.

Considerations related to equipoise in HIV cure research:

- In the context of HIV cure research, equipoise may become more important as HIV cure research strategies start showing signals of efficacy, and in later phase trials.
- There is no comparator or efficacious intervention in the HIV cure research field.
- An alternative to equipoise would be to focus on the risks that people are asked to incur as part of research and attempt to establish robust safety rules and clear futility signals in HIV cure studies.
- Other alternatives to equipoise relevant to HIV cure research include (a) evaluating all aspects of a clinical study, including motivations of study participants for joining the study, and ensuring that participation is nonexploitative (Miller & Brody, 2015); (b) examining protocols on a case-by-case basis, and asking for expert scientific and community review (Kimmelman, 2007); (c) appreciating considerations across the entire translational research continuum (Joffe & Miller, 2008); and (d) adopting a scientific orientation and methodological rigor and focusing on scientific and professional integrity (Joffe & Miller, 2008).

Considerations related to risk–benefit ratios in HIV cure research:

- Assessment of acceptable risk–benefit ratios in early HIV cure research are complex. Individual study participants bear the risks of research, while most benefits accrue to science and society. If risks are not justified by corresponding therapeutic benefits, the ethical permissibility of early-phase HIV cure studies rests on demonstrating prospects of significant scientific and societal benefits while minimizing potential harms. Biomedical HIV cure researchers are thus ethically obligated to design studies that will be informative and provide societal value. Minimizing risks to participants is crucial in minimizing the potential for exploitation in HIV cure research.
- Early-phase HIV cure clinical studies carry greater individual clinical risks than benefits. Most investigational interventions carry greater than minimal risks. Experiments will not be curative, and the incremental nature of the research should be appreciated.
- Risks of HIV cure research should be contextually assessed in terms of the investigational product/intervention, the type of study participants, the stage of disease, and the standard of care available. The perspectives of PLWHIV in what is a favorable risk–benefit assessment should be valued by clinician-researchers and policy-makers/bioethicists (Evans, 2017). Several PLWHIV perceive the likelihood of psychosocial benefits in early-phase HIV cure research.
- Ways of increasing ethical acceptability of risk–benefit ratios in early-phase HIV cure research have been proposed, including (a) reducing risks to participants, (b) enhancing benefits for participants, (c) focusing on voluntary and informed consent, and (d) emphasizing benefits to nonparticipants (Eyal, 2017a).

Considerations related to "otherwise healthy volunteers" in HIV cure research:

- Although the general FDA policy is to consider healthy PLWHIV as "otherwise healthy volunteers" for the purpose of assessing risks and benefits of HIV cure research for the field, it is important to remember that HIV cure research protocols should be evaluated on a case-by-case-basis in light of the latest scientific evidence.
- From an ethical standpoint, clinician-researchers involved in HIV cure research need to include proper protocol safeguards to minimize harms to the fullest. If harms occur, there should be robust procedures in place to mitigate these harms, as with other types of clinical research.
- It is important to remember that several PLWHIV may not consider themselves "healthy," even though they are virally suppressed. HIV cure research implementers should be careful not to produce additional health problems or vulnerabilities for PLWHIV, and should pay attention to perceived vulnerabilities and issues of stigma and discrimination.

Note. PLWHIV = people living with HIV; FDA = Food and Drug Administration.

risk and benefit questions. For example, clinician-researchers need to determine whether a study is designed well enough so that it will move the HIV cure research field forward with new knowledge. Policy-makers/bioethicists need to determine whether a study meets regulatory standards of risks and benefits. PLWHIV need to decide whether to participate in studies. In addition, our data may not be applicable to contexts outside of the United States, including resource-limited settings, where risks and benefits, values, background HIV treatment, and standard of care realities may differ. We interviewed each key informant only once. Longitudinal data collection would have allowed us to derive evolving perceptions of ethical concepts, including changes in risk–benefit ratios. Interviews focused on HIV cure research in general, as opposed to specific HIV cure research strategies.

Conclusion

In sum, this study yielded rich narratives around ethics concepts in the context of early-phase HIV cure research in the United States. Considering the critical role played by early-phase and translational HIV cure research in moving science forward, it is important to develop standards to evaluate the ethical permissibility of studies. The application of ethical principles can greatly influence considerations for regulatory and institutional review, informed consent, assessments of risks and benefits, and the selection of study participants in HIV cure research. We should appreciate issues that are uniquely posed by the search for a cure for HIV infection, including research conducted against a background of highly effective antiretroviral therapy and risky interventions performed in

"otherwise healthy volunteers." Our study revealed the need for critical reflection around topics such as equipoise, risk–benefit ratios, and the idea of "otherwise healthy volunteers." While a cure for HIV would yield a tremendous benefit for PLWHIV around the world, the process of testing possible interventions will be risky, particularly among people who enjoy relatively healthy, normal lives (Lo & Grady, 2013). The HIV cure research community has the opportunity to establish robust ethical standards and best practices that will benefit the field as a whole (Dresser, 2017). The search for a cure will continue and will require extensive community, stakeholder, and patient engagement. The success of any particular HIV cure study will crucially depend on gaining the trust of PLWHIV and community. Such trust will require assurance that studies are conducted responsibly. Only by appreciating the inherent complexities and nuances presented will we be able to resolve challenges involved in early-phase HIV cure clinical research and pave the way for an ethical odyssey toward a cure.

Educational Implications

Information about risks and benefits of HIV cure clinical studies should be made clearly available to potential study participants who need to make decisions about whether to participate in studies. Policy-makers/bioethicists who make decisions about whether HIV cure studies move forward should ensure that they have the information needed to make such decisions. Biomedical HIV cure researchers should ensure that risks and benefits of HIV cure studies are clearly reported. Mutual dialogue between HIV cure researchers and other stakeholders should be encouraged. Responsible and meaningful community engagement around HIV cure research requires ongoing and meaningful consultation with a variety of stakeholders. Educational initiatives that translate complex HIV cure science in lay terms, such as the CUREiculum (http://www.avac.org/cureiculum) effort, should be properly supported and encouraged. The CUREiculum is a collaborative project aimed at making HIV cure research science accessible to communities and the HIV research field, and an attempt to respond to the growing need for a reliable source of information on HIV cure-related research.

Best Practices

Standards for HIV cure research must be developed to evaluate the ethical permissibility of studies. This, in turn should be done with PLWHIV in collaboration with clinicians, bioethicists, and IRB members. HIV cure research often includes analytical treatment interruptions, which confer risks as most of the PLWHIV on treatment are "otherwise healthy" and lead otherwise healthy normal lives. This brings importance to the topics of risks and benefits when individuals participate in HIV cure research, and these topics should be highlighted in informed consent prior to participation. There should be a distinction between individual and societal risks–benefits, especially because there may be no clear measure of risk–benefit ratios in HIV cure research. Rigorous social science and empirical bioethics research studies are needed, together with ongoing dialogue between key stakeholders, including PLWHIV, clinicians, biomedical HIV cure researchers, and bioethicists, to inform the development of best practices for conducting HIV cure research.

Research Agenda

HIV cure research is unique in that it is conducted against a background of highly effective and potent antiretroviral therapy, raising the thresholds of safety, efficacy, and acceptability for potential HIV cure research interventions, some of which require the withdrawal of therapy. Future research will need to carefully consider the differences between research participants and researchers in their perceptions of the ethical permissibility of studies. Most importantly, it should seek to better understand how PLWHIV view cure research, such as the risks they would be willing to accept as study participants. For HIV cure research, conceptualizing benefits to individuals will need to include not only potential health benefits, but also personal and psychological benefits. Developing clear ways to discuss risks with PLWHIV is also a critical area of future research. Finally, how to select participants remains a question. Although individuals with well-managed HIV are typically considered "otherwise healthy," PLWHIV may view their health differently. Additional efforts to understand the views of both PLWHIV and other stakeholders regarding a variety of specific study conditions will deepen our understanding of these ethical issues and improve the direction of future biomedical cure research, and social sciences and ethics research as well.

Availability of Data and Material

Datasets analyzed in this study were collected by researchers using a standardized interview guide customized to each category of key informant: (a) clinician-researcher, (b) policy-maker/bioethicist, and (c) person living with HIV (PLWHIV).

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Notes

1. Unexpected clinical benefits have also been reported to occur in HIV cure research. For example, Sangamo-type trials have been associated with a benefits to the participant's baseline immune function (Dubé, Taylor, et al., 2017; Tebas et al., 2014).
2. The label indication for panobinostat (Farydak®) in refractory multiple myeloma is 20 mg given every other day or three doses per week for Weeks 1 and 2 of each 21-day cycle for eight cycles, in combination with bortezomib and dexamethasone. Although the mg dose was the same in the proposed panobinostat + alpha-interferon HIV cure study referred to above, there were important differences. The investigators were proposing to give three doses every 4 weeks, in contrast to six doses every 3 weeks, and did not intend to administer bortezomib and dexamethasone. Virally suppressed HIV-positive volunteers were considered "otherwise healthy" by the Food and Drug Administration (FDA) as opposed to cancer patients with multiple myeloma who have had at least two other types of treatment failure. The FDA directed the investigators to proceed with a single, 1-week course of panobinostat ± alpha-interferon, instead of three or four courses spaced 4 weeks apart. The FDA also required that an initial cohort of eight study participants on a 5 mg dose of panobinostat with six participants receiving panobinostat plus alpha-interferon and two receiving only panobinostat. The second cohort of eight study participants will receive 10 mg of panobinostat, six of whom will also receive alpha-interferon and two who will not. The final cohort of 15 study participants will receive a 15 mg dose of panobinostat with 10 receiving alpha-interferon and five receiving panobinostat alone. The FDA will not permit investigators to administer the 20 mg dose before reviewing the data from all three cohorts. The FDA also tightened eligibility requirements, in particular requiring stress echocardiograms to rule out any clinically unsuspected cardiac condition.

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